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CHEST Recent Advances in Chest Medicine

Exhaled Nitric Oxide in Pulmonary Diseases

A Comprehensive Review

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The upregulation of nitric oxide (NO) by inflammatory cytokines and mediators in central and peripheral airway sites can be monitored easily in exhaled air. It is now possible to estimate the predominant site of increased fraction of exhaled NO (FeNO) and its potential pathologic and physiologic role in various pulmonary diseases. In asthma, increased FeNO reflects eosinophilic-mediated inflammatory pathways moderately well in central and/or peripheral airway sites and implies increased inhaled and systemic corticosteroid responsiveness. Recently, five randomized controlled algorithm asthma trials reported only equivocal benefits of adding measurements of FeNO to usual clinical guideline management including spirometry; however, significant design issues may exist. Overall, FeNO measurement at a single expiratory flow rate of 50 mL/s may be an important adjunct for diagnosis and management in selected cases of asthma. This may supplement standard clinical asthma care guidelines, including spirometry, providing a noninvasive window into predominantly large-airway-presumed eosinophilic inflammation. In COPD, large/central airway maximal NO flux and peripheral/small airway/alveolar NO concentration may be normal and the role of FeNO monitoring is less clear and therefore less established than in asthma. Furthermore, concurrent smoking reduces FeNO. Monitoring FeNO in pulmonary hypertension and cystic fibrosis has opened up a window to the role NO may play in their pathogenesis and possible clinical benefits in the management of these diseases.

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Abbreviations: ASTRAL = asthma randomized treatment algorithm studies; CANO = peripheral/small airway/alveolar nitric oxide concentration; CF = cystic fibrosis; cNOS = constitutive nitric oxide synthase; FeNO = fraction of exhaled oxygen; ICS = inhaled corticosteroids; iPAH = idiopathic pulmonary arterial hypertension; J'awNO = large/central airway maximal nitric oxide flux; NO = nitric oxide; NOS = nitric oxide synthase; NOS1 = neuronal nitric oxide synthase; NOS2 = inductible nitric oxide synthase; NOS3 = endothelial nitric oxide synthase; PAH = pulmonary arterial hypertension; ppb = parts per billion; RCT = randomized controlled trial

Nitric oxide (NO) is produced by resident cells (eg, airway epithelial cells, airway and circulatory endothelial cells, and trafficking inflammatory cells) in both large and peripheral airways and alveoli. The fraction of exhaled NO (FeNO) can be measured easily and is well established in research, with > 2,000 peer-reviewed publications on FeNO and its increasing adoption into clinical practice. This review builds on a previous review on the practical aspects of FeNO in asthma care[1] with the goal of updating the reader on the pathologic roles of NO in inflammatory airway disease, covering new ways to model NO exchange in the large and small airways/alveoli that can identify the anatomic location of NO production, and then reviewing FeNO measurement in asthma, pulmonary hypertension, cystic fibrosis (CF), and COPD.

NO as a Mediator of Inflammatory Airway Disease

Endogenous NO plays a critical role in regulating airway function and has both beneficial and detrimental effects on airway function. NO is a gaseous signaling molecule that is generated by three isoenzymes of NO synthase (NOS) that are differentially regulated and expressed in the airways and appear to play different pathophysiologic roles.[2]

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NO Synthases

All NOS isoenzymes convert L-arginine to L-citrulline with the generation of NO. Constitutive NOS (cNOS) isoenzymes include neuronal NOS (NOS1) and endothelial NOS (NOS3), both of which are activated by calcium ions to produce small amounts of NO, which is presumed to play a local regulatory role, such as neurotransmission (NOS1) and regulation of local blood flow (NOS3). Inducible NOS (NOS2) is not constitutively expressed but is induced by inflammatory and infectious stimuli and produces large amounts of NO independent of calcium ion influx, which may have a proinflammatory effect. However, the clear distinction between constitutive and inducible isoforms has been blurred by the recognition that cNOS may be inducible, whereas NOS2 may be constitutively expressed in some conditions. Nevertheless, these distinct NOS isoenzymes are regulated by different genes and have different physiologic and pathologic functions. Selective inhibitors of these isoforms are now becoming available, which will make it easier to examine their different roles. There are important species differences, particularly in the regulation of NOS2, which is readily induced in rodent cells, but has been more difficult to induce in human cells. Corticosteroids directly suppress NOS2 in rodent cells, but do not directly inhibit NOS2 expression in human airway epithelial cells.[3] The increase in NO in exhaled breath in asthma is presumed to originate from increased NOS2 expression in the respiratory tract, although cNOS isoforms may also contribute.

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Endothelial NOS

NOS3 is expressed in endothelial cells of the bronchial and pulmonary circulation and plays a role in regulating vascular flow.[4] It is also expressed in alveolar endothelial cells and airway epithelial cells throughout the respiratory tract. NOS3 may play a role in reducing plasma exudation in the airways,[5] whereas epithelial NOS3 may regulate ciliary beating and, therefore, mucociliary clearance.[2] Defective NOS3 function may contribute to airway hyperresponsiveness in animal models of asthma.[2] NOS3 is only active as a homodimer, and S-nitrosylation, as a result of oxidative stress, reduces dimerization and enzyme activity.[6] NOS3 in alveolar endothelial cells may contribute to peripheral NO. NOS3 expression is reduced in the peripheral lung of patients with COPD, especially in severe disease due to alveolar wall destruction as a result of emphysema.[7]

Neuronal NOS

NOS1 is localized to cholinergic nerves in the airways and mediates inhibitory nonadrenergic noncholinergic neural bronchodilatation, acting as a functional antagonist of its cotransmitter, acetylcholine.[8] Arginase, which shows increased activity in asthma, reduces NO synthesis by NOS1, resulting in increased neuronal bronchoconstriction.[9] NOS1 is also expressed in airway epithelial cells and type 1 pneumocytes, and there is evidence that its expression and activity are increased in the peripheral lungs of COPD patients as a result of oxidative stress.[9] In mice, ozone exposure results in increased NOS1 expression in the lung, leading to increased formation of NO.[10] This suggests that NOS1 may contribute to the increase in peripheral NO in COPD and severe asthma that has been reported.[11,12]

Inducible NOS

Increased NOS2 expression is found in the airway epithelial cells of patients with asthma and is reduced by inhaled corticosteroids (ICS).[13] Increased NOS2 expression is also found in the peripheral lung and small airways in patients with COPD.[7,14] Oxidative stress generates superoxide anions and, in combination with NO, may result in the formation of the highly reactive species peroxynitrite, which is increased in the exhaled breath condensate of COPD patients[15] and may account for the increased tyrosine nitration found in the peripheral lungs by immunocytochemistry.[14] The formation of peroxynitrite removes NO from the gaseous phase so that its concentration in the airways is reduced when there is a high level of oxidative stress, as in COPD patients. Selective inhibitors of NOS2

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reduce FeNO in asthmatic patients and even in normal subjects,[16-18] but have less effect in COPD patients, indicating that the increased peripheral NO may derive from NOS1 as well as NOS2 in these patients.

Modeling of NO Excretion in the Lungs

Exhaled NO was first detected in the exhaled breath of mammals in 1991,[19] and by 1997, with the first report of a strong inverse dependence on the exhalation flow,[20] it was clear that the exchange dynamics were unique. Hence, previous quantitative frameworks to understand the exchange principles of gases such as oxygen, carbon dioxide, nitrogen, and water would need to be advanced significantly.[21] Since 1998, numerous research groups have made significant contributions toward our fundamental understanding of NO exchange dynamics in the lungs through the creation of not only mathematic models, but also new experimental algorithms to test, validate, and characterize the model parameters. Modeling enables increased and decreased NO excretion to be evaluated in different pathologic sites (eg, larger airways vs peripheral lung).

The observation that FeNO concentration was inversely related to the exhalation flow was consistent with a fixed volume source; that is, as exhalation flow increases, the contact time of the airstream with a surface serving as a source of NO would be reduced, creating an inverse dependence on the flow. Hence, the relatively rigid conducting airways were a plausible source of NO in the exhaled breath. If the airways were the only source of NO, then one would predict that the product of FeNO and flow (ie, the elimination rate of NO) would be constant over a wide range of flows; however, early experimental observations demonstrated that the elimination rate of NO was a positive function of exhalation flow,[22] consistent with a source of NO from a region of the lung that changes volume during exhalation. For example, as a balloon deflates, the concentration of a gas within the balloon will not change; hence, if a balloon deflates faster (ie, increase in exhalation flow), the elimination rate will increase. In other words, the observation that the elimination rate of NO was a positive function of exhalation flow was also consistent with a source of NO in the alveolar region. These principles formed the foundation of the two-compartment model (ie, an airway compartment and an alveolar compartment) of NO exchange, first reported in 1998[23] and later confirmed by four additional independent research groups.[24-27]

In the simplest form, the two-compartment model can be characterized by two parameters: a maximal flux of NO from the large airway compartment (J'awNO; nL/s; airway generations 1-16) and a steady-state mean distal airway/alveolar concentration of NO (CANO; parts per billion [ppb]). A series of experimental algorithms characterized by measuring FeNO at different constant exhalation flows has been presented and reviewed.[28] Although the simplicity of the initial two-compartment model is a tremendous strength, recent work has demonstrated that axial back-diffusion of NO in the gas phase (ie, NO back-diffusing from airways toward the alveolar region against the direction of exhalation) cannot be neglected.[29-32] Incorporating axial gas phase back-diffusion of NO produces a two-compartment model with more complex governing equations and modified algorithms to characterize J'awNO and CANO.[33,34] For example, a simple method used widely to determine J'awNO and CANO is to regress a line through a plot of the elimination rate of NO vs the exhalation flow; the intercept and slope are estimates of J'awNO and CANO, respectively ("slope-intercept" method).[23] When axial back-diffusion of NO in the gas phase is considered, NO from the airway tree diffuses back ("back-diffusion") into the alveolar region, where it can falsely elevate the estimate of CANO and depress the estimate of J'awNO. Thus, the modified algorithm using the slope-intercept method still uses the slope to estimate CANO, but subtracts a term proportional to the airway flux (J'awNO/0.53) to account for axial diffusion; similarly, the estimate for J'awNO remains the intercept but is multiplied by a factor (1.7) to account for the loss to the alveolar region.[33]

Clinical interest in modeling NO exchange dynamics, which have the ability to discriminate between J'awNO and CANO, remains strong because of the potential clinical usefulness of measuring and determining the predominant site of eosinophilic airway inflammation.[35,36] Applying this modeling, various results have been reported in mild and moderate-to-severe disease.[11,34-40] Our understanding of NO exchange dynamics continues to evolve, and additional factors such as heterogeneity in structure and ventilation patterns in the lungs[41] may also prove to be important considerations as we move toward a more complete understanding of the NO pulmonary exchange.

From the practical viewpoint, FeNO obtained at 50 mL/s according to American Thoracic Society/European Respiratory Society guidelines[42] is a reliable surrogate of J'awNO and has proven to be very useful in asthma, as described in the next section. However, there is no simple surrogate for determining CANO because FeNO needs to be obtained at multiple expiratory flow rates and for using the aforementioned algorithm[32,33] to determine J'awNO and CANO.

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Exhaled NO in Asthma

Historically, the assessment of patients with obstructive lung diseases such as asthma and COPD has focused on lung function measurements. However, particularly in mild disease, most patients do not demonstrate spirometric abnormalities. An alternative perspective, provided by a biomarker reflecting underlying inflammatory activity, is potentially helpful.[43] In this regard, measuring FeNO may have practical clinical applications in selected patients because it is precise and reproducible and provides immediate results.

Simplistically, FeNO measurements are considered a surrogate for eosinophilic airway inflammation. However, correlations with sputum eosinophils are modest. In the largest population studied, the r^2 value was 0.26 ($P = .001$); the sensitivities and specificities for clinically significant eosinophilia were around 70% to 75%.[44] Despite this apparent limitation, this is still an important observation because eosinophilic airway inflammation is characteristically steroid responsive.[45] Thus, in most patients, high FeNO (> 45 ppb) may be regarded as a marker for steroid responsiveness,[46,47] including improvement in spirometry and airway hyperresponsiveness.[48] This is arguably the most important information that can be gained from a single FeNO measurement, especially in a patient with undiagnosed airway symptoms. Conversely, a low FeNO (< 25 ppb in adults) has a high predictive value for the absence of eosinophilic airway inflammation (85%)[49] and, in turn, for a poor response to steroid.[50] Importantly, the relationship between FeNO and airway inflammation is independent of the diagnosis of asthma as defined by airway hyperresponsiveness and variable respiratory symptoms. FeNO is not a diagnostic test for asthma as such. Increased FeNO may occur with eosinophilic bronchitis[51] and in some patients with COPD.[52] Furthermore, serial FeNO measurements may yield information that is not available from single measurements (eg, with exposure to sensitizing agents or allergens).[53]

Predicted values for FeNO are derived from population-based reference equations.[54-58] Factors such as age (children < 12 years), sex, atopy and current cigarette smoking need to be taken into account when determining what is "normal." Tall, elderly, atopic, nonsmoking males are likely to have the highest values. The distribution is skewed to the right but, overall, the upper limit of "normal" for all comers is as high as 45 ppb. This corresponds to the upper limit of the 95% CI in a population of patients with clinically stable asthma.[55] It also corresponds to the cut point of 45 to 50 ppb for ICS responsiveness noted in clinical studies.[48] Although reducing FeNO levels to "normal" would seem to be desirable, achieving "personal best" FeNO (obtained when a patient is receiving oral steroid therapy) or "normal" FeNO measurements (based on predicted values) is not necessary to achieve good asthma control.[59] Indeed, in some individuals, FeNO may remain persistently high despite improved spirometry and good asthma control.[60]

FeNO levels increase during exacerbations of asthma.[61] They decrease or increase following up- and down-titration or withdrawal of ICS therapy[62,63] and with leukotriene receptor antagonists.[64] Recently, five randomized control trials (RCTs) have prospectively evaluated whether using FeNO levels to guide antiinflammatory therapy in predominantly mild-to-moderate asthma improves clinical outcomes. The results have been equivocal at best.[49,65-68] However, there are potential issues with the design of these studies that are discussed in the next section of this review, and elsewhere.[69] These results do not mean that FeNO has no role in the management of asthma. Although routine measurements of FeNO for clinical management may not be indicated, FeNO may provide a useful adjunct to conventional tools, particularly when asthma is "difficult to treat." The test is best used to clarify the cause of symptoms where more than one factor may be operant (see Table 1). For example, in an anxious, obese asthmatic patient with poor control, knowing that FeNO is either high (> 50 ppb) or low (< 25 ppb) may be helpful (lower values apply in children < 12 years old). If FeNO is high and the patient is symptomatic, then presumed eosinophilic inflammation is probably uncontrolled. Improving treatment adherence and/or increasing the dose of ICS or initiating tapering oral corticosteroid are options. If FeNO is normal/low, and spirometry is normal or has not changed, then issues relating specifically to obesity and/or anxiety need to be addressed. Alternatively, in the presence of airflow obstruction and normal/low FeNO, noneosinophilic airway inflammation needs to be considered, and other treatment options applied. This example highlights the fact that where symptoms and inflammation are discordant, measuring inflammation will provide useful information.[70] Monitoring changes in individual patients over time may shed further light.[71] There is also evidence that future risk of poor asthma control is related to increased FeNO, especially when spirometry is abnormal.[37] Overall, FeNO measurement at a single expiratory flow rate of 50 mL/s provides a noninvasive window into presumed eosinophilic inflammation. This is a potentially helpful adjunct in the assessment and management of asthmatics, especially in complex cases.

Randomized Algorithm Studies in Asthma

Recent studies[49,65-68] that have compared add-on FeNO to clinical guideline management, asthma randomized treatment algorithm studies (ASTRAL),

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Table 1—*A General Guideline as to the Significance of FeNO Levels in Patients With an Established Diagnosis of Asthma*

	FeNO < 25 ppb (< 20 ppb in children)	FeNO 25-50 ppb (20-35 ppb in children)	FeNO > 50 ppb (> 35 ppb in children)
Symptoms present	Consider alternative diagnoses Unlikely to benefit from increase in ICS	Persistent allergen exposure Inadequate ICS dose Poor compliance Steroid resistance	Persistent allergen exposure Poor compliance or inhaler technique Inadequate ICS dose At risk for exacerbation Steroid resistance
Symptoms absent	Adequate ICS dose Good compliance; consider ICS taper or even withdrawal	Adequate ICS dosing Good compliance Monitor change in FeNO	ICS withdrawal or dose reduction may result in relapse Poor compliance or inhaler technique

Serial measurement may yield more appropriate cut points for individual patients. Clinical decisions based on results of FeNO need to correlate with spirometry and dose of ICS. FeNO = fraction of exhaled oxygen; ICS = inhaled corticosteroid.

have been equivocal for the use of FeNO to reduce asthma exacerbations or improve asthma control. However, there may have been significant design issues for many of these studies that may have led to incorrect conclusions.[69] ASTRAL studies, such as the FeNO studies, require different methodologic design features from a traditional RCT that are optimized to test drug efficacy, and these are summarized here.

First, an ASTRAL trial should recruit a broad population in terms of severity and level of therapy, unlike a drug-efficacy RCT. The studies using induced sputum used this approach and showed superiority over conventional management.[72] A well- and easily-controlled population that experiences few exacerbations will be unlikely to show benefit from, nor require sophisticated techniques such as, FeNO. Detecting poor compliance is a major benefit of using FeNO, but the clinical trial setting commonly excludes poor adherence to therapy.

The use of FeNO to guide therapy in asthma has been compared with guideline-driven management based on asthma-control measures. However, in some studies, a composite of FeNO and clinical assessment has been used.[46,55,58,59,66] Blinded treatment allocation and outcome assessment are crucial if the comparison is to be free from bias. After trial completion, the two management strategies should be analyzed for discordance or concordance at each decision point in the trial, usually at the study visits. This can be expressed as the discordance/concordance ratio.[69] If this ratio is low, then the two randomized strategies do not differ and will not result in differences in asthma outcomes, and the reason for this needs to be analyzed. This has not been reported systematically in the current FeNO studies, but when calculated for some studies it was low, suggesting a methodologic reason for an inconclusive study.[69]

The treatment algorithm can be complex to apply in a clinical trial, and selection of cut points is crucial and may influence outcomes. The clinical guidelines-driven strategies rely on the level of asthma control (eg, diary symptom scores, rescue medication, nighttime awakenings, and lung function measured in the clinic). The available asthma-control systems differ greatly among the various studies and have not been validated for predictive value. To establish whether the algorithm could possibly be effective, the discordance/concordance ratio of the treatment algorithm should be evaluated during pilot assessment of any potential algorithm.

The cut points used for FeNO in each study were not tested in pilot studies of any of the monitoring studies. There is considerable variation in FeNO levels among clinically stable patients, as there is for lung function, and perhaps the optimal way would be to determine the stable level for each individual by giving a short prednisone burst before the trial and use that in the algorithm. In other words, individual cut points are probably more effective than fixed cut points in addressing interindividual variability; no studies to date have done this. Furthermore, the inclusion of more than one cut point is advantageous (eg, separate cut points for increasing and reducing therapy). Another approach is to look for changes from baseline rather than a cut point.[73]

In all recent FeNO-guided therapy studies, a step-up and step-down hierarchy of treatments was applied in the randomized strategies. For this to be effective, and able to detect a treatment effect, initially there should be a dose-response relationship for the outcomes of interest (eg, ICS and asthma exacerbations). When the dose-response relationships are flat,[74] dose increments in the algorithm should probably be wide ranging, with multiple steps, including prednisone. Long-acting β-2 agonists were included in the strategy in some studies and may synergize with inhaled steroids to prevent exacerbations. However, because of the weak potency of leukotriene-modifying agents and theophylline on exacerbations, these agents probably add little to the treatment intervention.

The choice of study outcomes is important. Asthma exacerbations are probably the most relevant primary outcome. The parameters used for the algorithm treatment decision (eg, asthma control) must not also be used as outcome measures (teleologic error). For example, if asthma control is used in the clinical strategy

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to adjust therapy, then it cannot also be used as an outcome measure, and another outcome (eg, asthma exacerbations, Asthma Quality of Life Questionnaire, or another outcome) should be used to assess the efficacy of the treatment strategy. The study needs to be powered adequately for the outcomes of interest. Improved adherence, as commonly occurs in a clinical trial, may reduce the incidence of outcomes (eg, exacerbations) and the study may not end up adequately powered.

In summary, ASTRAL FeNO studies with equivocal results[49,65-68] have significant design issues that may cast doubt on the validity of their findings. The true value of FeNO in improving asthma control and reducing exacerbations has yet to be tested rigorously.

Exhaled NO in Pulmonary Hypertension

Pulmonary arterial hypertension (PAH) is a hemodynamic state characterized by elevation of the pulmonary arterial pressure and is associated with increased pulmonary vascular resistance, leading to deterioration in cardiopulmonary function and premature death.[75] PAH is commonly caused by, or associated with, an underlying pulmonary or systemic disease. When PAH is present in the absence of an identifiable cause or associated underlying disease, it is referred to as idiopathic PAH (IPAH) or primary pulmonary hypertension. A familial form of IPAH accounts for about 6% of cases.[75] Most of our understanding about the pathobiology of pulmonary hypertension is based on studying IPAH, which is characterized by endothelial and smooth muscle cell proliferation, medial hypertrophy, and thrombosis in situ.[76] The elevated pulmonary vascular resistance seems to result from an imbalance between locally produced vasodilators and vasoconstrictors, in addition to cellular proliferation and vascular remodeling.[76,77]

The discovery that the endothelium-derived relaxing factor was NO,[78,79] a simple, highly diffusible, gaseous molecule, resulted in a paradigm shift in our understanding of the pulmonary circulation. The lung is a major source of NO, be it from NOS3 in the endothelium of the vast pulmonary circulation, NOS2 in the epithelium of the large surface area of the airways, or NOS1 in the nonadrenergic noncholinergic nerves.[80] The unique lung anatomy with the close proximity of the airways to the blood vessels allows NO that is produced in high levels in the upper and lower airways by NOS2 to affect the pulmonary vascular tone in concert with the low NO levels that are produced by NOS3 in the vascular endothelium.[80,81] Although the vascular endothelium produces large amounts of NO, very little, if any, is exhaled. This is because of the rapid affinity of NO to hemoglobin in the pulmonary circulation, which effectively acts as a sink for NO produced by the vascular endothelium.[80] Once produced by the airway epithelium or the vascular endothelium, NO is freely diffusible and enters pulmonary vascular smooth muscle cells to activate soluble guanylate cyclase and produce guanosine 3′,5′-cyclic monophosphate, resulting in vascular smooth muscle relaxation and vasodilation.

NO is one of the important pathophysiologic mediators of pulmonary hypertension.[77,81] In addition to vasodilation, NO regulates endothelial cell proliferation and angiogenesis, and maintains overall vascular health.[82] Interestingly, patients with PAH have low FeNO values.[82] Individuals with PAH also have lower than normal concentrations of NO reaction products in the BAL fluid, which is inversely related to the degree of pulmonary hypertension.[83] Furthermore, replacement of NO seems to work well in treating the problem.[81] Although the administration of NO as an inhaled gas in the treatment of pulmonary hypertension is cumbersome and impractical outside the hospital setting or the catheterization laboratory, therapies that target the NO pathway have revolutionized the treatment of this disease. One example is the widely used phosphodiesterase type 5 inhibitors, which prevent the breakdown of the NO effector molecule 3′,5′-cyclic guanosine monophosphate, thus prolonging NO effects on tissues.[84,85] The NO deficiency state in patients with PAH also improves with other therapies that do not directly target the NO pathway, like prostacyclins and endothelin receptor antagonists.[86] This seems to also have a prognostic significance, with improved survival in patients who respond to therapy with a higher FeNO level compared with those who do not change their NO levels in response to therapy.[84] The low FeNO levels in patients with PAH and the improvement following effective therapeutic intervention suggest that serial monitoring may be useful. Further study will be required to establish the usefulness of FeNO in these settings.

Exhaled NO in CF

CF is characterized by abnormal ion transport across the respiratory epithelium, resulting in increased airway mucus viscosity, chronic infection, and inflammation. Unlike in other inflammatory airway diseases such as asthma, FeNO is typically decreased in CF patients.[87] Flow-independent NO exchange parameters such as J'awNO are also altered in CF patients. One study suggested that airway NO diffusion capacity was elevated in CF and airway wall and CANO were reduced,[88] whereas others have reported CANO to be increased in CF patients compared with controls.[89] Reduction of NO formation in CF is associated with severe CF

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transmembrane regulator gene mutations, pancreatic insufficiency, airway obstruction, and *Pseudomonas* infection.[90]

The expression of NOS2 is reduced in CF airway epithelial cells, and attenuated NOS2 expression is believed to favor lower airway infection with *Pseudomonas aeruginosa*.[91] The observation that "low-producer" variants in cNOS genes were associated with increased risk for *P aeruginosa* infections in CF patients suggests that the emergence of *P aeruginosa* in CF is related to low-airway NO formation in general and is not specific to NOS2 deficiency.[92]

The substrate for NOS is the amino acid L-arginine, which is also the substrate for arginases. Arginase activity is increased in CF sputum[93] and is believed to result in reduced availability of L-arginine for NO synthesis in CF airways.[94] Consistent with this hypothesis, inhalation of nebulized L-arginine significantly increased FeNO in CF patients.[88,95] Low FeNO is associated with poor pulmonary function in CF patients.[94] In support of a functional correlation between airway NO and airflow, inhaled nebulized L-arginine, which resulted in an increase in FeNO, also significantly improved FEV_1 in patients with CF.[96] Similarly, antibiotic treatment that improves pulmonary function in CF patients also increases FeNO.[97] However, individual responses are highly variable and the relationship of FeNO and pulmonary function is not strong enough to use FeNO as a marker of CF lung disease. Using the two-compartment model,[22] recent studies have reported a link between reduced FeNO and reduced bronchial flux J'awNO but normal CANO in adult CF patients;[98] however, these results were based on a small sample size and the study did not exclude atopic individuals. Therefore, although there is considerable interest in better understanding abnormalities in NO-related metabolism and its contribution to CF lung disease, FeNO has not yet been shown to be a useful clinical marker in CF patient care.

Exhaled NO in COPD

COPD is an inflammatory disease of both large and small airways and alveoli that is predominantly mediated by cytokines and interleukins via neutrophilic cellular pathways.[99] In stable COPD, FeNO measurements need to be obtained in concurrent nonsmokers to avoid misleading reduction in FeNO. When measured at a single expiratory flow rate, FeNO has been elevated[52,100,101] or normal[2] and increased with exacerbations.[102,103] Papi et al[102] and Kunisaki et al[103] reported that an elevated FeNO in severe COPD may also be a signal for spirometric response to ICS. In a randomized trial, Siva et al[104] successfully used sputum eosinophils compared with standard care as a tool to reduce severe COPD exacerbations. In that study, sputum eosinophils and FeNO were not associated, possibly because of the interaction of ICS and concurrent smoking, both of which independently suppress FeNO. Despite these conflicting findings, measurement of J'awNO and CANO via modeling[23] may potentially detect increased large-airway NO flux, and allow selection of individual COPD patients who may benefit from ICS.

Using the two-compartment NO model as previously described[23] and without correction for NO axial back-diffusion,[33,34] we,[37,38] Berry et al,[105] van Veen et al,[106] Brindicci et al,[11] and other investigators[34-40] have noted increased J'awNO and increased CANO in mild and moderate-to-severe clinically stable asthmatics. Using similar NO modeling[23] and without correction for NO axial back-diffusion,[33,34] Högman et al[107] and Brindicci et al[12] reported increased J'awNO, as well as increased CANO, in clinically stable COPD patients compared with controls. However, in the study by Brindicci et al,[12] their healthy nonsmoking controls had a mean age of 45 years, compared with their COPD cohort with a mean age of 62 years. This may have confounded their findings, because we have noted that normal younger subjects, aged < 50 years, have significantly lower values for CANO compared with older normals, aged > 60 years.[37,38] However, in a subsequent study, Brindicci et al[7] reported increased messenger RNA expression and activity of isoenzyme nNOS in peripheral lung tissue that reflected the severity of the disease. Although Högman at al[107] used age-matched controls, neither Högman et al[107] nor Brindicci et al[12] corrected for axial back-diffusion of NO from large airways to peripheral lung.[33,34] This underestimates J'awNO and overestimates CANO. After correction, J'awNO will increase and CANO will decrease.[33,34] We[108] recently compared COPD patients to age-matched controls using the two-compartment model[23] and, after correcting for NO axial back-diffusion,[33] found normal values for J'awNO and CANO. Furthermore, we[108] noted that moderate-dose, but not low-dose, ICS could suppress normal values for J'awNO. Previously, Roy et al[109] noted normal J'awNO and CANO in COPD patients compared with age-matched healthy, older, nonsmoking subjects, but without correcting for NO axial back-diffusion.[33] Finally, Dummer et al[110] also reported FeNO at 50 mL/s, a surrogate for J'awNO, was a weak predictor of increase in FEV_1 (liters) following short-term steroid response in moderate-to-severe COPD patients with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 2 and 3 disease. In conclusion, in COPD, the role of FeNO monitoring is less clear and therefore less established than in asthma. Furthermore, concurrent smoking reduces FeNO, and may provide spurious results.

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Summary

The upregulation of NO by inflammatory cytokines and mediators in central and peripheral airway sites can be monitored easily in exhaled air. It is now possible to estimate the predominant site of increased FeNO and its potential pathologic and physiologic role in various pulmonary diseases. In asthma, increased FeNO reflects eosinophilic-mediated inflammatory pathways moderately well in central and or peripheral airway sites and implies increased inhaled and systemic corticosteroid responsiveness. Recently, five randomized controlled algorithm asthma trials have reported only equivocal benefits of adding measurements of FeNO to usual clinical guideline management including spirometry; however, significant design issues may exist. Overall, FeNO measurement at a single expiratory flow rate of 50 mL/s may be an important adjunct for diagnosis and management in selected cases of asthma. This may supplement standard clinical asthma care guidelines including spirometry, providing a noninvasive window into predominantly large-airway-presumed eosinophilic inflammation. In COPD, J'awNO and CANO may be normal and the role of FeNO monitoring is less clear and therefore less established than in asthma. Furthermore, concurrent smoking reduces FeNO. Monitoring FeNO in pulmonary hypertension and CF has opened up a window to the role NO may play in their pathogenesis and its possible clinical benefits in managing these diseases.

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Financial/nonfinancial disclosure: The authors have reported to *CHEST* the following conflicts of interest: Dr George has patents issued and pending that have been licensed in the past by Aerocrine, Ltd., Sweden, and have resulted in royalties. His employer, University of California, Irvine, has received NO analyzers as gifts from Aerocrine, Ltd., and currently holds the rights to the patents. Dr Silkoff has received royalties ($2,000/year) from patents that are currently licensed to GE Analytical Instruments, Inc, and Aperion Inc, manufacturers of exhaled NO monitors. He has also received consultant fees ($10,000) from GE Analytical Instruments, Inc, Aperion Inc, and Aerocrine, Ltd. He anticipates being involved in patent litigation related to measurement of exhaled NO. Dr Zamel has received royalties ($2,000/year) from patents that are currently licensed to Aerocrine, Ltd. and Aperion Inc, manufacturers of exhaled NO monitors. Dr Taylor has received research funding ($25,000) and lecture fees ($2,000) from Aerocrine, Ltd., Sweden. Drs Barnes, Dweik, Gelb, Gibson Grasemann, Pavord, and Ratjen have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

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